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* * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *
FILE 'HOME' ENTERED AT 14:16:36 ON 09 JUL 2002

=> file ca

=> s cyclooxygenase 2
         15113 CYCLOOXYGENASE
       7203441 2
L1        2999 CYCLOOXYGENASE 2
                 (CYCLOOXYGENASE(W)2)

=> s l1 and inhibit?
       1461721 INHIBIT?
L2        2287 L1 AND INHIBIT?

=> s 5 lipoxygenease inhibit?
       5090270 5
            11 LIPOXYGENEASE
       1461721 INHIBIT?
L3           2 5 LIPOXYGENEASE INHIBIT?
                 (5(W)LIPOXYGENEASE(W)INHIBIT?)

=> s 5-lipoxygenase
       5090270 5
         13521 LIPOXYGENASE
L4        4077 5-LIPOXYGENASE
                 (5(W)LIPOXYGENASE)

=> s immunosuppressive
L5       13166 IMMUNOSUPPRESSIVE

=> s anti-proliferative
        263806 ANTI
         27718 PROLIFERATIVE
L6        1047 ANTI-PROLIFERATIVE
                 (ANTI(W)PROLIFERATIVE)

=> s anit-inflammatory
           210 ANIT
         86006 INFLAMMATORY
L7           1 ANIT-INFLAMMATORY
                 (ANIT(W)INFLAMMATORY)

=> s leukocyte
L8       60635 LEUKOCYTE

=> s l5 or l6 or l7 or l8
L9       74230 L5 OR L6 OR L7 OR L8

=> s l9 and l1 and l3
L10          0 L9 AND L1 AND L3

=> s l9 and l1 and l4
L11          8 L9 AND L1 AND L4

=> s l1 and l4
L12         61 L1 AND L4

=> s l1 and l9
L13         95 L1 AND L9
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=> s l4 and l9
L14        589 L4 AND L9

=> s l12 and l13
L15          8 L12 AND L13

=> s l12 and combin?
        790201 COMBIN?
L16          7 L12 AND COMBIN?

=> s l13 and combin?
        790201 COMBIN?
L17         10 L13 AND COMBIN?

=> s l15 and combin?
        790201 COMBIN?
L18          1 L15 AND COMBIN?

=> s l16 or l17 or l18
L19         16 L16 OR L17 OR L18

=> d ibib abs 1-16

L19  ANSWER 1 OF 16  CA  COPYRIGHT 2002 ACS
ACCESSION NUMBER:        136:84447  CA
TITLE:                   Inhibition of the mitogen activated protein kinase,
                         p38.alpha., prevents proinflammatory cytokine
                         induction by human adherent mononuclear leukocytes in
                         response to lipid loading
AUTHOR(S):               Feng, Y.; Schreiner, G. F.; Chakravarty, S.; Liu, D.
                         Y.; Joly, A. H.
CORPORATE SOURCE:        Scios Inc., Sunnyvale, CA, 94086, USA
SOURCE:                  Atherosclerosis (Shannon, Ireland) (2001), 158(2),
                         331-338
                         CODEN: ATHSBL; ISSN: 0021-9150
PUBLISHER:               Elsevier Science Ireland Ltd.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
```

AB Macrophage infiltration, inflammatory processes, and oxidatively modified low d. lipoprotein (LDL) are known contributing factors in the formation of the atherosclerotic plaque. To det. whether a direct link might exist between these factors, the authors examd. the effect of oxidized LDL upon proinflammatory cytokine prodn. in adherent human peripheral blood mononuclear leukocytes. Oxidized LDL, as well as a **combination** of cholesterol and 25-hydroxycholesterol, induced tumor necrosis factor-.alpha. (TNF.alpha.) and interleukin-1.beta. (IL-1.beta.) mRNA as measured by quant. real time PCR, by a max. of 2-4-fold following a 24-h incubation. Anal. of cell culture supernatants revealed a concomitant stimulation of TNF.alpha. and IL-1.beta. secreted protein as detd. by ELISA. Treatment of human peripheral blood mononuclear leukocytes with oxidized LDL or the **combination** of cholesterol and 25-hydroxycholesterol caused activation of p38.alpha. as detd. by the ability of immunopptd. p38 to phosphorylate an ATF-2 fusion protein, a surrogate substrate of p38.alpha.. VK-19911 (Pyridine, 4-[4-(4-fluorophenyl)-1-(4-piperidinyl)-1H-imidazol-5-yl]-dihydrochloride), a specific inhibitor of p38.alpha., prevented the induction of TNF.alpha. and IL-1.beta. by oxidized LDL in a dose-dependent manner. Activated p38.alpha. is known to be involved in the stabilization of **cyclooxygenase-2** mRNA in response to stimuli such

as lipopolysaccharide; however, in the setting of oxidized LDL-induced p38.alpha. activation, COX-2 mRNA levels were not affected. Taken together, the data imply a potential role for p38.alpha. activation in lipid-assocd. inflammatory processes.

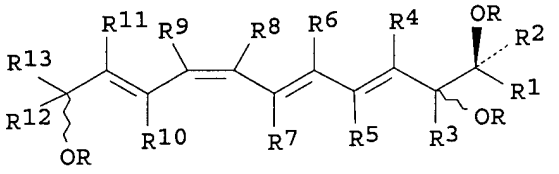
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 16 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 135:272792 CA
TITLE: Lipoxin analogs and their use for the treatment of periodontal disease
INVENTOR(S): Van Dyke, Thomas E.; Petasis, Nicos A.; Serhan, Charles N.
PATENT ASSIGNEE(S): Trustees of Boston University, USA; Brigham and Women's Hospital; University of Southern California
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001070664	A2	20010927	WO 2001-US9096	20010320

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-190656P P 20000320
OTHER SOURCE(S): MARPAT 135:272792
GI



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AB This invention provides new lipoxin analogs, such as, I [R = H, (un)satd. alkyl; R1,R2, R12, R13 = H, substituted alkyl, aryl, heteroaryl,cycloalkyl, alkoxy, halo, aryl, carboxy, carboxamido; R3 = H, substituted alkyl, aryl, heteroaryl,cycloalkyl, alkoxy, halo, aryl, carboxy, carboxamido; R4-R11 = H, halo, un(substituted) alkyl, substituted aryl, heteroaryl, cycloalkyl, alkoxy, halo, aryl, carboxy, carboxamido; R1-R13 = a bond that forms a carbon-carbon double bond, a carbon-carbon triple bond, or a ring with lipoxin backbone; R, R1-R13 independently join in any **combination** to form one or more rings contg. 3 to 20 carbon atoms, wherein the rings optionally contain 1 to 6 oxygen atoms, 1 to 6 nitrogen atoms, or 1 to 6 oxygen atoms and 1 to 6 nitrogen atoms], compns. contg. these analogs, and methods of using these compds. and

compns. for treating and preventing oral inflammation, including gingivitis, periodontitis, and other forms of periodontal disease with compns. contg. COX-2 inhibitors. Further, the invention provides methods for preventing systemic diseases beyond the oral cavity that are related to periodontal disease using the compns. contg. lipoxin analogs, COX-2 inhibitors, or both.

L19 ANSWER 3 OF 16 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 135:190408 CA
TITLE: Aspirin-triggered lipid mediators
INVENTOR(S): Serhan, Charles N.; Clish, Clary B.
PATENT ASSIGNEE(S): The Brigham and Women's Hospital, Inc., USA
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001060778	A2	20010823	WO 2001-US5196	20010216
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002055538	A1	20020509	US 2001-785866	20010216

PRIORITY APPLN. INFO.: US 2000-183078P P 20000216
US 2000-238814P P 20001006

OTHER SOURCE(S): MARPAT 135:190408

AB Aspirin triggered lipid mediators are disclosed which are useful for the treatment or prevention of inflammation assocd. with various diseases, including ischemia. The present invention provides that inflammatory exudates from mice treated with .omega.-3 PUFA and aspirin generate a novel array of bioactive lipid signals. Human endothelial cells with upregulated COX-2 treated with aspirin converted C20:5 w-3 to 18R-HEPE and 15R-HEPE. Each was used by polymorphonuclear leukocytes to generate sep. classes of novel trihydroxy-contg. mediators, including 15R-lipoxin and 5,12,18R-triHEPE. These compds. were potent inhibitors of human polymorphonuclear **leukocyte** transendothelial migration and infiltration in vivo.

L19 ANSWER 4 OF 16 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 135:175361 CA
TITLE: Treatment or prevention of prostate cancer with a COX-2 selective inhibiting drug
INVENTOR(S): Waldstreicher, Joanne; Morrison, Briggs W.
PATENT ASSIGNEE(S): Merck + Co., Inc., USA
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001060365	A1	20010823	WO 2001-US4655	20010213
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2001041713	A1	20011115	US 2001-784878	20010216
PRIORITY APPLN. INFO.:			US 2000-183204P P	20000217

AB A COX-2 selective inhibiting drug is disclosed as useful in treating or preventing prostate cancer. The compd. is used alone or in **combination** with other drugs.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 5 OF 16 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 135:33472 CA
TITLE: Preparation of sulfamoylheteroaryl pyrazole compounds as anti-inflammatory and analgesic agents
INVENTOR(S): Ando, Kazuo; Kawamura, Kiyoshi
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 71 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1104760	A1	20010606	EP 2000-310441	20001124
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001163883	A2	20010619	JP 2000-366780	20001201
BR 2000005703	A	20010731	BR 2000-5703	20001204
PRIORITY APPLN. INFO.:			US 1999-168889P P	19991203
OTHER SOURCE(S):		MARPAT 135:33472		

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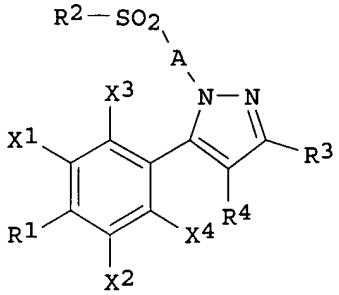

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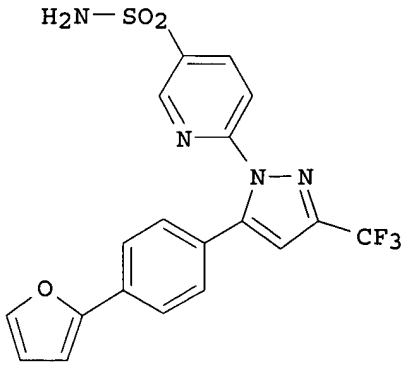


II

AB Title compds. (I) [wherein A and R1 = independently (un)substituted 5-6 membered heteroaryl ring which may be fused to a 5-7 membered carbocyclic or 5-6 membered heteroaryl ring; R2 = NH2; R3 and R4 = independently H, halo, CN, NO2, CO2H, CONH2, or (un)substituted alkyl, alkenyl, alkoxy, alkylcarbonyl, alkoxycarbonyl, (di)alkylaminocarbonyl, or N-alkyl-N-(hetero)arylaminocarbonyl; X1, X2, X3, and X4 = independently H, halo, OH, CN, SH, CO2H, NO2, CONH2, or (un)substituted alkyl(thio), alkoxy, (di)alkylamino, alkylcarbonyl, or alkoxycarbonyl] were prepd. as **cyclooxygenase-2** (COX-2) inhibitors. For example, 6-chloro-3-pyridinesulfonamide was treated with anhyd. hydrazine and dissolved in 10% methanolic HCl to give the 6-hydrazino dihydrochloride (84.5%). Refluxing furan-2-boronic acid, Pd(PPh3)2Cl2, and satd. NaHCO3 soln. with 4,4,4-trifluoro-1-(4-bromophenyl)butane-1,3-dione for 5 h gave the 2-furylphenyl deriv. (61.2%). Heating the hydrazine with the butanedione to reflux temp. for 18 h afforded the cycloaddn. product (II) in 11.5% yield. In either canine or human in vitro COX-2 assays, I inhibited COX-2 with IC50 values of 0.001 .mu.M to 3 .mu.M. I are useful in the treatment of pain, inflammation, and other diseases and conditions mediated by COX-2.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 6 OF 16 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 135:14030 CA
TITLE: Mitigation of arthritis by high-dose administration of a COX-2 inhibitor in the collagen-induced arthritis model in the mouse
AUTHOR(S): Obukowicz, Mark G.; Ornberg, Richard L.
CORPORATE SOURCE: Discovery Pharmacology, G. D. Searle, St. Louis, MO, 63167, USA
SOURCE: Advances in Experimental Medicine and Biology (1999), 469(Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation, and Radiation Injury, 4), 145-150
CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Non-steroidal anti-inflammatory drugs (NSAIDs), including selective **cyclooxygenase-2** (COX-2) inhibitors, improve many parameters of arthritis in the adjuvant-induced arthritis model in the rat. However, results with NSAIDs in the collagen-induced arthritis model in the mouse have been equivocal, possibly due to a mechanism that is prostaglandin-independent and because the level of dosing is limited due

to gastrointestinal (GI) toxicity. With the advent of selective COX-2 inhibitors, it was possible to evaluate the efficacy of high-level dosing of a COX-2 inhibitor in the context of a GI-sparing background. A study was conducted to evaluate whether SC-046, a selective COX-2 inhibitor, mitigates the incidence and/or severity of arthritis and, possibly, is disease-modifying in the collagen-induced arthritis model in the mouse. SC-046 mitigated visual incidence and severity and histopathol. scores of arthritis in a dose-dependent manner. It also caused redns. in the anti-collagen antibody titer at doses >10 mpk, bid, whether dosing was initiated prophylactically on day 0 or on day 21, just before the onset of visible arthritis on day 26. These results suggest that the mechanism of action, may in part, be due to the **immunosuppressive** properties of SC-046 at high doses. However, the data do not support immune modulation by SC-046 during the initiation phase of the immune response. **Combined** COX-2/COX-1 inhibition could be responsible for the complete mitigation of arthritis at high doses, either by partial immunosuppression or by yet unknown mechanisms beyond inhibition of prostaglandin synthesis.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 7 OF 16 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 134:361399 CA
TITLE: Use of thiazole derivatives for treatment/prevention of p38 kinase-mediated disorders
INVENTOR(S): Ingelman-Sundberg, Magnus; Simi, Anastasia; Tindberg, Niclas
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001035959	A1	20010525	WO 2000-SE2252	20001115

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: SE 1999-4177 A 19991118
OTHER SOURCE(S): MARPAT 134:361399

AB The present invention relates to the thiazole derivs., geometrical and optical isomers, tautomers and racemates thereof where such isomers or tautomers exist, as well as pharmaceutically acceptable acid addn. salts thereof and solvates thereof, for the prepn. of a medicament for the treatment and/or prevention of p38 MAP kinase-mediated disorders, such as inflammation, neurol. disorders, hepatic diseases, arthritis, cachexia, autoimmune diseases, endotoxic shock, ophthalmic diseases, etc. The thiazole compds. have been evaluated biol. (1) in rat cortical glial cultures, (2) in human neuroblastoma cell lines, and (3) in in vitro immunocomplex kinase assays. The results showed that the imidazole deriv. 4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole

(SB 203580), but not 5-(2-chloroethyl)-4-methylthiazole (clomethiazole) or 1-(4-methyl-5-thiazolyl)-1-phenylmethylamine, inhibited p38 MAP kinase in this assay. The results demonstrate that the thiazole compds. of the invention and imidazole derivs. such as SB 203580 act by different mechanisms when interfering with p38 MAP kinase pathways.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 8 OF 16 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 133:359009 CA
TITLE: Inhibitory effect of citrus nobiletin on phorbol ester-induced skin inflammation, oxidative stress, and tumor promotion in mice
AUTHOR(S): Murakami, Akira; Nakamura, Yoshimasa; Torikai, Koji; Tanaka, Takuji; Koshiba, Teruaki; Koshimizu, Koichi; Kuwahara, Shigeru; Takahashi, Yasuo; Ogawa, Kazunori; Yano, Masamichi; Tokuda, Harukuni; Nishino, Hoyoku; Mimaki, Yoshihiro; Sashida, Yutaka; Kitanaka, Susumu; Ohigashi, Hajime
CORPORATE SOURCE: Department of Biotechnological Science, Faculty of Biology-Oriented Science and Technology, Kinki University, Wakayama, 649-6493, Japan
SOURCE: Cancer Research (2000), 60(18), 5059-5066
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The intake of citrus fruits has been suggested as a way to prevent the development of some types of human cancer. Nitric oxide (NO) is closely assocd. with the processes of epithelial carcinogenesis. We attempted a search for NO generation inhibitors in Citrus unshiu. The active constituent was traced by an activity-guiding sepn. NO and superoxide (O2-) generation was induced by a **combination** of lipopolysaccharide and IFN-.gamma. in mouse macrophage RAW 264.7 cells, and by 12-O-tetradecanoylphorbol-13-acetate (TPA) in differentiated human promyelocyte HL-60, resp. Expression of inducible NO synthase and **cyclooxygenase 2** proteins were detected by Western blotting. The in vivo anti-inflammatory and antitumor promoting activities were evaluated by topical TPA application to ICR mouse skin with measurement of edema formation, epidermal thickness, **leukocyte** infiltration, hydrogen peroxide prodn., and the rate of proliferating cell nuclear antigen-stained cells. As a result, nobiletin, a polymethoxyflavonoid, was identified as an inhibitor of both NO and O2- generation. Nobiletin significantly inhibited two distinct stages of skin inflammation induced by double TPA application [first stage priming (**leukocyte** infiltration) and second stage activation (oxidative insult by leukocytes)] by decreasing the inflammatory parameters. It also suppressed the expression of **cyclooxygenase-2** and inducible NO synthase proteins and prostaglandin E2 release. Nobiletin inhibited dimethylbenz[a]anthracene (0.19 .mu.mol)/TPA (1.6 nmol)-induced skin tumor formation at doses of 160 and 320 nmol by reducing the no. of tumors per mouse by 61.2% ($P < 0.001$) and 75.7% ($P < 0.001$), resp. The present study suggests that nobiletin is a functionally novel and possible chemopreventive agent in inflammation-assocd. tumorigenesis.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 9 OF 16 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 133:321880 CA
TITLE: Treatment of inflammation and inflammation-related

disorders with a **combination** of a **cyclooxygenase-2** inhibitor and a **5-lipoxygenase** inhibitor.

INVENTOR(S): Isakson, Peter C.; Anderson, Gary D.; Gregory, Susan A.

PATENT ASSIGNEE(S): G. D. Searle & Co., USA

SOURCE: U.S., 21 pp., Cont.-in-part of U.S. Ser. No. 489,472, abandoned.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

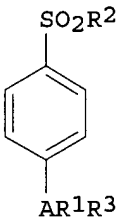
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6136839	A	20001024	US 1996-661660	19960611
CA 2224517	AA	19961227	CA 1996-2224517	19960611

PRIORITY APPLN. INFO.: US 1995-489472 B2 19950612

OTHER SOURCE(S): MARPAT 133:321880

GI



I

AB A **combination** comprising a **5-lipoxygenase** inhibitor and a **cyclooxygenase-2** inhibitor selected from title compds. [I; A = pyrazolyl; R1 = .gtoreq.1 of (substituted) heterocyclyl, cycloalkyl, cycloalkenyl, aryl; R2 = Me, amino; R3 = H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, CO2H, cyanoalkyl, heterocyclyloxy, alkoxy, alkylthio, alkylcarbonyl, aryl, haloalkyl, etc.], is claimed. Thus, EtO2CCHF2 in MeOCMe3 was treated with NaOMe and then with 3-fluoro-4-methoxyacetophenone (prepn. given) followed by 16 h stirring to give 96% 4,4-difluoro-1-(3-fluoro-4-methoxyphenyl)butane-1,3-dione. This was refluxed 16 h with 4-sulfonamidophenylhydrazine hydrochloride in EtOH to give 87% 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide (II). II with 6-[[3-fluoro-5-(3,4,5,6-tetrahydro-4-methoxy-2H-pyran-4-yl)phenoxy]methyl]-1-methyl-1H-quinazolin-2-one (III) at 30 mpk/day orally in mice in the collagen-induced arthritis screen reduced incidence of arthritis to 20% (vs. 100% for controls). A formulation contg. II and III is given.

REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 10 OF 16 CA COPYRIGHT 2002 ACS

ACCESSION NUMBER: 129:135541 CA

TITLE: Arachidonic acid enhances the tissue factor expression of mononuclear cells by the cyclo-oxygenase-1 pathway: beneficial effect of n-3 fatty acids

AUTHOR(S): Cadroy, Yves; Dupouy, Dominique; Boneu, Bernard
CORPORATE SOURCE: Lab. Recherche l'Hemostase Thrombose, Centre Hospitalo-Universitaire, Toulouse, 31059, Fr.
SOURCE: Journal of Immunology (1998), 160(12), 6145-6150
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Monocytes express tissue factor (TF) upon stimulation by inflammatory agents. Dietary administration of fish oil rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) results in a impairment of TF expression by monocytes. EPA and DHA are metabolized differently from arachidonic acid (AA), the major fatty acid present in cell membranes. We examd. the effects of AA on the TF expression of isolated human PBMC, and we detd. whether EPA and DHA modulated this phenomenon differently. Nonstimulated PBMC had a low TF-dependent procoagulant activity. When PBMC were incubated with increasing concns. of AA, the TF-dependent procoagulant activity increased in a dose-dependent manner to 190% at 7.5 .mu.M. Indomethacin, a cyclooxygenase inhibitor, totally abolished the stimulating effect of AA, whereas specific pharmacol. inhibitors of **cyclooxygenase-2** or of **5-lipoxygenase** had no inhibitory effect. A thromboxane (TX)A2/endoperoxides receptor antagonist and a TX synthase inhibitor blocked the potentiating effect of AA. Purified PGG2 and carbocyclic TXA2, TXA2 agonist, enhanced the procoagulant activity of PBMC in a dose-dependent manner whereas, in contrast, PGE2 inhibited it. Finally, contrary to AA, EPA or DHA did not increase TXB2 prodn. or TF expression by PBMC. The TF-dependent procoagulant activity of isolated PBMC was increased by AA through the prodn. of cyclooxygenase-1 metabolites; the **combined** action of PGG2 and TXA2, which potentiated it, was greater than that of PGE2, which inhibited it. Dietary n-3 fatty acids exert part of their beneficial effect by modulating this procoagulant activity differently from AA.

L19 ANSWER 11 OF 16 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 128:252514 CA
TITLE: New **Cyclooxygenase-2/5-Lipoxygenase** Inhibitors. 1. 7-tert-Butyl-2,3-dihydro-3,3-dimethylbenzofuran Derivatives as Gastrointestinal Safe Antiinflammatory and Analgesic Agents: Discovery and Variation of the 5-Keto Substituent
AUTHOR(S): Janusz, John M.; Young, Patricia A.; Ridgeway, James M.; Scherz, Michael W.; Enzweiler, Kevin; Wu, Laurence I.; Gan, Lixian; Darolia, Renuka; Matthews, Randall S.; Hennes, Duane; Kellstein, David E.; Green, Shelley A.; Tulich, Jennifer L.; Rosario-Jansen, Theresa; Magrisso, I. Jack; Wehmeyer, Kenneth R.; Kuhlenbeck, Deborah L.; Eichhold, Thomas H.; Dobson, Roy L.; Sirko, Steven P.; Farmer, Ralph W.
CORPORATE SOURCE: Health Care Research Center, Procter Gamble Pharmaceuticals, Mason, OH, 45040, USA
SOURCE: Journal of Medicinal Chemistry (1998), 41(7), 1112-1123
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of 5-keto-substituted 7-tert-butyl-2,3-dihydro-3,3-dimethylbenzofurans (DHDMBFs) were prepd. and evaluated as potential nonsteroidal antiinflammatory and analgesic agents. Interest in this

class of compds. arose when a DHDMBF was found to be an active metabolite of the di-tert-butylphenol antiinflammatory agent tebufelone. It was found that a variety of 5-keto-substituted DHDMBFs have good in vivo antiinflammatory and analgesic activity after oral administration. These compds. inhibit both cyclooxygenase (COX) and **5-lipoxygenase** (5-LOX) in vitro. The cyclooxygenase inhibition was found to be selective for the **cyclooxygenase-2** isoform, and this **combination** of COX-2/5-LOX inhibition may be responsible for the gastrointestinal safety of compds. such as 30.

L19 ANSWER 12 OF 16 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 127:239123 CA
TITLE: **Combinations** having **immunosuppressive** effects, containing **cyclooxygenase-2**-inhibitors and **5-lipoxygenase** inhibitors
INVENTOR(S): Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
PATENT ASSIGNEE(S): G.D. Searle & Co., USA; Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9729776	A1	19970821	WO 1997-US1558	19970212
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2246265	AA	19970821	CA 1997-2246265	19970212
AU 9718505	A1	19970902	AU 1997-18505	19970212
EP 888127	A1	19990107	EP 1997-904133	19970212
EP 888127	B1	20011212		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2000504723	T2	20000418	JP 1997-529363	19970212
AT 210461	E	20011215	AT 1997-904133	19970212
US 6376528	B1	20020423	US 1999-430072	19991018

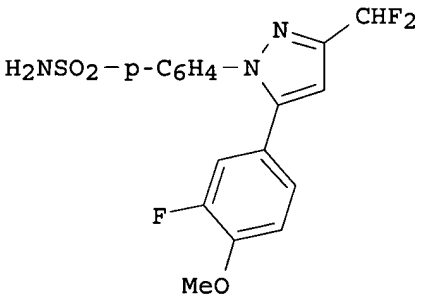
PRIORITY APPLN. INFO.: US 1996-600622 A1 19960213
WO 1997-US1558 W 19970212
US 1998-189463 B1 19981110
OTHER SOURCE(S): MARPAT 127:239123
AB Treatment with a **cyclooxygenase-2** inhibitor and a **5-lipoxygenase** inhibitor is described as being useful in reducing recipient rejection of transplanted organs and for treatment of autoimmune diseases. 4-[5-(3-Fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide and N'-[3-[5-(4-fluorophenoxy)-2-furyl]-1-methyl-2-propynyl]-N'-hydroxyurea were prepd. and a **combination** of these 2 compds. showed a delay in rejection time of skin grafts while treatment alone of each of these compds. resulted in no prolongation of graft survival.

L19 ANSWER 13 OF 16 CA COPYRIGHT 2002 ACS

ACCESSION NUMBER: 127:225303 CA
TITLE: **Immunosuppressive combinations** containing a **cyclooxygenase-2** inhibitor and a leukotriene A4 hydrolase inhibitor
INVENTOR(S): Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
PATENT ASSIGNEE(S): G.D. Searle & Co., USA; Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9729774	A1	19970821	WO 1997-US1421	19970211
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2246336	AA	19970821	CA 1997-2246336	19970211
AU 9719525	A1	19970902	AU 1997-19525	19970211
EP 880363	A1	19981202	EP 1997-907545	19970211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2001506574	T2	20010522	JP 1997-529358	19970211
US 6407140	B1	20020618	US 2000-489311	20000121

PRIORITY APPLN. INFO.: US 1996-600655 A1 19960213
WO 1997-US1421 W 19970211
OTHER SOURCE(S): MARPAT 127:225303
GI



I

AB Immunosuppressant compns. contg. a **combination** of a **cyclooxygenase-2** inhibitor (which inhibits conversion of arachidonic acid to prostaglandins) and a LTA4 hydrolase inhibitor are useful in reducing recipient rejection of transplanted organs and for treatment of autoimmune diseases. Thus, F2CHCO2Et reacted with 3-fluoro-4-methoxyacetophenone to form 4,4-difluoro-1-(3-fluoro-4-methoxyphenyl)butane-1,3-dione, which was condensed with

4-sulfonamidophenylhydrazine-HCl to produce the **cyclooxygenase-2** inhibitor I. A formulation was prepd. contg. 350 mg I and 700 mg 3-[N-methyl-N-[3-[(4-phenylmethyl)phenoxy]propyl]amino]propanoic acid (LTA4 hydrolase inhibitor).

L19 ANSWER 14 OF 16 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 127:189616 CA
TITLE: Chemokine and **cyclooxygenase-2** expression in human endometrium coincides with **leukocyte** accumulation
AUTHOR(S): Jones, Rebecca L.; Kelly, Rodney W.; Critchley, Hilary O. D.
CORPORATE SOURCE: Department of Obstetrics and Gynaecology, University of Edinburgh, Edinburgh, EH3 9EW, UK
SOURCE: Human Reproduction (1997), 12(6), 1300-1306
CODEN: HUREEE; ISSN: 0268-1161
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The endometrium contains a resident population of leukocytes, the no. and subtype of which vary throughout the menstrual cycle and in early pregnancy. Factors controlling these fluctuations are unknown, but a **combination** of proliferation in situ and migration from the vasculature has been proposed. Locally acting inflammatory mediators, including specific chemokines and prostaglandins, have been implicated in these processes. Interleukin-8 (IL-8) and monocyte chemoattractant protein-1 (MCP-1) are potent chemoattractants and activators for neutrophils and monocytes resp. Locally acting prostaglandins modulate vascular permeability, and a synergistic action of prostaglandin E (PGE) with IL-8 has been described. Here, IL-8, MCP-1, and **cyclooxygenase-2** (COX-2), the inducible isoform of prostaglandin synthase, were all localized in the endometrium by immunohistochem. throughout the menstrual cycle and in early pregnancy. All 3 inflammatory mediators were localized to the perivascular cells of blood vessels in endometrium and decidua, and addnl. immunoreactivity for COX-2 was identified in the glandular epithelium. The intensity of immunostaining was reduced in the periovulatory, early and mid-secretory phases and increased premenstrually. These results further support the hypothesis that there is a premenstrual migration of leukocytes into the endometrium mediated by chemokines.

L19 ANSWER 15 OF 16 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 126:166479 CA
TITLE: Compositions comprising a **cyclooxygenase-2** inhibitor and a **5-lipoxygenase** inhibitor for treatment of inflammation and inflammation-related disorders
INVENTOR(S): Isakson, Peter C.; Anderson, Gary D.; Gregory, Susan A.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9641626	A1	19961227	WO 1996-US10106	19960611

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN

CA 2224517	AA	19961227	CA 1996-2224517	19960611
AU 9661117	A1	19970109	AU 1996-61117	19960611
EP 833622	A1	19980408	EP 1996-918465	19960611
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 11507670	T2	19990706	JP 1997-503273	19960611
PRIORITY APPLN. INFO.:			US 1995-489472 A	19950612
			WO 1996-US10106 W	19960611

OTHER SOURCE(S): MARPAT 126:166479

AB **Combinations** of a **cyclooxygenase-2** inhibitor and a **5-lipoxygenase** inhibitor are described for treatment of inflammation and inflammation-related disorders. Prepn. of e.g. 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is described., as are pharmaceutical formulations and activity against collagen-induced arthritis in mice.

L19 ANSWER 16 OF 16 CA COPYRIGHT 2002 ACS

ACCESSION NUMBER: 125:292089 CA

TITLE: Pharmacology of meloxicam, a new non-steroidal anti-inflammatory drug with an improved safety profile through preferential inhibition of COX-2

AUTHOR(S): Engelhardt, G.

CORPORATE SOURCE: Department Biological Research, Dr Karl Thomae GmbH, Biberach, D-88400, Germany

SOURCE: Br. J. Rheumatol. (1996), 35(Suppl. 1), 4-12
CODEN: BJRHDF; ISSN: 0263-7103

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 69 refs. is presented on key pharmacol. findings of a new non-steroidal anti-inflammatory drug (NSAID), meloxicam. Unlike established NSAIDs, meloxicam preferentially inhibits inducible COX-2 in guinea-pig peritoneal macrophages and human COX-2 in COS cells. Compared with other NSAIDs, meloxicam is the most potent inhibitor of prostaglandin biosynthesis in pleural and peritoneal exudate, but only a weak inhibitor in the gastric tract and kidney. Ulcerogenicity in the rat stomach is weak in relation to anti-inflammatory potency, resulting in a high therapeutic index. Meloxicam's high anti-inflammatory potency **combined** with good tolerability can be explained by its preferential inhibition of COX-2. In adjuvant arthritis rats, meloxicam inhibits not only paw swelling, but also bone and cartilage destruction and systemic signs of disease. It inhibits **leukocyte** migration, but has no effect on leukotriene B4 or C4. Meloxicam shows a long-lasting anti-inflammatory and analgesic effect on inflammatory pain and reduces pyrogen-induced fever, but has no central nervous system effects. The pharmacokinetic profile of meloxicam in the rat is similar to that in man. Metabolites are inactive.

=> file medline

==> s l1

16577	CYCLOOXYGENASE
2431178	2
L20 3883	CYCLOOXYGENASE 2 (CYCLOOXYGENASE(W)2)

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=> s l4
       1689221 5
          9973 LIPOXYGENASE
L21       3095 5-LIPOXYGENASE
                 (5(W)LIPOXYGENASE)

=> s l5
L22      49173 IMMUNOSUPPRESSIVE

=> s l6
        367876 ANTI
         47392 PROLIFERATIVE
L23       1140 ANTI-PROLIFERATIVE
                 (ANTI(W)PROLIFERATIVE)

=> s l7
           268 ANIT
        170500 INFLAMMATORY
L24          2 ANIT-INFLAMMATORY
                 (ANIT(W)INFLAMMATORY)

=> s l8
L25      83095 LEUKOCYTE

=> s l22 or l23 or l24 or l25
L26     131838 L22 OR L23 OR L24 OR L25

=> s l20 and l21
L27         61 L20 AND L21

=> s l27 and l26
L28          8 L27 AND L26

=> d ibib abs 1-8

L28  ANSWER 1 OF 8     MEDLINE
ACCESSION NUMBER:   2002106668     MEDLINE
DOCUMENT NUMBER:    21670914   PubMed ID: 11811948
TITLE:              Arachidonic and linoleic acid metabolism in mouse
                    intestinal tissue: evidence for novel lipoxygenase
                    activity.
AUTHOR:             Kawajiri Hiroo; Hsi Linda C; Kamitani Hideki; Ikawa
                    Hiroshi; Geller Mark; Ward Toni; Eling Thomas E; Glasgow
                    Wayne C
CORPORATE SOURCE:   Eicosanoid Biochemistry Section, National Institutes of
                    Health, Research Triangle Park, North Carolina 27709, USA.
SOURCE:             ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (2002 Feb 1) 398
                    (1) 51-60.
                    Journal code: 0372430. ISSN: 0003-9861.
PUB. COUNTRY:       United States
                    Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200202
ENTRY DATE:         Entered STN: 20020213
                    Last Updated on STN: 20020216
                    Entered Medline: 20020215
AB   Previous studies in our laboratory revealed a high expression of
     15-lipoxygenase-1 in human colorectal carcinomas, suggesting the
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importance of lipoxygenase in colorectal tumor development. In this report, we have investigated the metabolism of arachidonic and linoleic acid by intestinal tissues of Min mice, an animal model for intestinal neoplasia. The polyp and normal tissues from Min mice intestine were homogenized, incubated with arachidonic or linoleic acid, and analyzed by reverse-, straight-, and chiral-phase HPLC. Arachidonic acid was converted to prostaglandins E2 and F2alpha. Little 12- or 15-hydroxyeicosatetraenoic acid was detected. Cyclooxygenase (COX)-2 was detected in polyps and the adjacent normal tissues by Western immunoblotting, but neither COX-1 nor **leukocyte**-type 12-lipoxygenase, the murine ortholog to human 15-lipoxygenase-1, was detected. These tissue homogenates converted linoleic acid to an equal mixture of 9(S)- and 13(S)-hydroxyoctadecadienoic acid (HODE). Inhibition of lipoxygenase activity with nordihydroguaiaretic acid blocked HODEs formation, but the COX inhibitor indomethacin did not. Degenerative-nested PCR analyses using primers encoded by highly conserved sequences in lipoxygenases detected **5-lipoxygenase**, **leukocyte**-type 12-lipoxygenase, platelet-type 12-lipoxygenase, 8-lipoxygenase, and epidermis-type lipoxygenase-3 in mouse intestinal tissue. All of these PCR products represent known lipoxygenase that are not reported to utilize linoleic acid preferentially as substrate and do not metabolize linoleic acid to an equal mixture of 9(S)- and 13(S)-HODE. This somewhat unique profile of linoleate product formation in Min mice intestinal tissue suggests the presence of an uncharacterized and potentially novel lipoxygenase(s) that may play a role in intestinal epithelial cell differentiation and tumor development.

L28 ANSWER 2 OF 8 MEDLINE
ACCESSION NUMBER: 2001199351 MEDLINE
DOCUMENT NUMBER: 21183293 PubMed ID: 11289660
TITLE: Inhibition of **5-lipoxygenase** activity by the natural anti-inflammatory compound aethiopinone.
AUTHOR: Benrezzouk R; Terencio M C; Ferrandiz M L; Hernandez-Perez M; Rabanal R; Alcaraz M J
CORPORATE SOURCE: Department of Pharmacology, University of Valencia, Faculty of Pharmacy, Spain.
SOURCE: INFLAMMATION RESEARCH, (2001 Feb) 50 (2) 96-101. Journal code: 9508160. ISSN: 1023-3830.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB OBJECTIVE AND DESIGN: We have investigated the mechanisms of action of aethiopinone, an anti-inflammatory compound from Salvia aethiopis L. roots. MATERIAL AND SUBJECTS: Human neutrophils from healthy volunteers and murine peritoneal macrophages. Swiss mice were randomly divided into groups of six animals. Treatment: Test compounds were applied topically in the mouse ear oedema test. In the air pouch, mice received aethiopinone (0.001-0.5 pmol/pouch or 12.5-50 mg/kg p.o.). METHODS: LTB4 production was assayed in human neutrophils and COX-2 and iNOS activities in murine macrophages. Air pouches were induced subcutaneously in mice and injected with zymosan on the day six. Mouse ear oedema was induced by arachidonic acid. Dunnett's t-test was employed for statistical analysis. RESULTS: We have observed potent inhibitory effects on human neutrophil LTB4 production without effects on COX or NOS activities. Aethiopinone is an in vitro inhibitor of 5-LO from human neutrophils (IC50 = 0.11 microM). In

addition, aethiopinone reduced **leukocyte** accumulation and showed in vivo inhibitory activity on this enzyme. CONCLUSIONS: Our results indicate that inhibition of 5-LO could participate in the anti-inflammatory properties of this natural product.

L28 ANSWER 3 OF 8 MEDLINE
ACCESSION NUMBER: 2000499355 MEDLINE
DOCUMENT NUMBER: 20431760 PubMed ID: 10973816
TITLE: Hinokitiol, a selective inhibitor of the platelet-type isozyme of arachidonate 12-lipoxygenase.
AUTHOR: Suzuki H; Ueda T; Juranek I; Yamamoto S; Katoh T; Node M; Suzuki T
CORPORATE SOURCE: Department of Biochemistry, Tokushima University School of Medicine, Kuramoto-cho, Tokushima, 770-8503, Japan.. suzuki@basic.med.tokushima-u.ac.jp
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2000 Sep 7) 275 (3) 885-9.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001027
Last Updated on STN: 20001027
Entered Medline: 20001019

AB Hinokitiol (4-isopropyltropolone), a constituent of Japanese cypress, reversibly inhibited platelet-type 12-lipoxygenase with an IC(50) of 0.1 microM, and the enzyme activity was almost lost at 1 microM. The compound was much less active with other lipoxygenase enzymes with higher IC(50) values (**leukocyte**-type 12-lipoxygenase, 50 microM; soybean lipoxygenase, 17 microM; 15-lipoxygenase-1, >100 microM; **5-lipoxygenase**, 17 microM). Hinokitiol up to 100 microM had almost no effect on cyclooxygenases-1 and -2. Their structure-activity relationship examined with various tropolone derivatives indicated the requirements of the 2-hydroxyl group and 4-alkyl group for the potent and selective inhibition of platelet-type 12-lipoxygenase.

L28 ANSWER 4 OF 8 MEDLINE
ACCESSION NUMBER: 2000412007 MEDLINE
DOCUMENT NUMBER: 20304650 PubMed ID: 10844115
TITLE: An anti-inflammatory ditriazine inhibiting **leukocyte** functions and expression of inducible nitric oxide synthase and cyclo-oxygenase-2.
AUTHOR: Rioja I; Ubeda A; Terencio M C; Guillen I; Riguera R; Quintela J M; Peinador C; Gonzalez L M; Alcaraz M J
CORPORATE SOURCE: Departamento de Farmacologia, Universidad de Valencia, Facultad de Farmacia, Av. Vicent Andres Estelles s/n, 46100 Burjasot, Valencia, Spain.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (2000 May 26) 397 (1) 207-17.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000907
Last Updated on STN: 20000907

Entered Medline: 20000829

AB A ditriazine derivative (4,10-dichloropyrido[5,6:4,5]thieno[3,2-d':3, 2-d]-1,2,3-ditriazine (DTD)) inhibited neutrophil functions, including degranulation, superoxide generation, and leukotriene B(4) production, without any effect on **5-lipoxygenase** activity. This compound reduced nitric oxide (NO) and prostaglandin E(2) production in mouse peritoneal macrophages stimulated with lipopolysaccharide, whereas no influence on the activity of inducible NO synthase, cyclo-oxygenase-2 or cyclo-oxygenase-1 was observed. DTD significantly reduced mouse paw oedema induced by carrageenan and also markedly reduced NO and prostaglandin E(2) levels in exudates from 24-h zymosan-stimulated mouse air pouch. Western blot analysis showed that DTD reduced the expression of inducible NO synthase and cyclo-oxygenase-2. Our results indicate that DTD exerts anti-inflammatory effects related to the inhibition of neutrophil functions and of NO and prostaglandin E(2) production, which could be due to a decreased expression of inducible NO synthase and cyclo-oxygenase-2.

L28 ANSWER 5 OF 8 MEDLINE
ACCESSION NUMBER: 2000233719 MEDLINE
DOCUMENT NUMBER: 20233719 PubMed ID: 10769133
TITLE: Lipoxin A(4) analogues inhibit **leukocyte** recruitment to Porphyromonas gingivalis: a role for **cyclooxygenase-2** and lipoxins in periodontal disease.
AUTHOR: Pouliot M; Clish C B; Petasis N A; Van Dyke T E; Serhan C N
CORPORATE SOURCE: Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: DE-06436 (NIDCR)
GM-38765 (NIGMS)
SOURCE: BIOCHEMISTRY, (2000 Apr 25) 39 (16) 4761-8.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000613
Last Updated on STN: 20000613
Entered Medline: 20000601

AB The potential involvement of the inducible cyclooxygenase isoform (COX-2) and the role of novel lipid mediators were investigated in the pathogenesis of periodontal disease. Crevicular fluids from localized juvenile periodontitis (LJP) patients contained prostaglandin (PG)E(2) and **5-lipoxygenase**-derived products, leukotriene B(4), and the biosynthesis interaction product, lipoxin (LX)A(4). Neutrophils from peripheral blood of LJP patients, but not from asymptomatic donors, also generated LXA(4), suggesting a role for this immunomodulatory molecule in periodontal disease. To characterize host responses of interest to periodontal pathogens, Porphyromonas gingivalis was introduced within murine dorsal air pouches. In the air pouch cavity, P. gingivalis elicited **leukocyte** infiltration, concomitant with elevated PGE(2) levels in the cellular exudates, and upregulated COX-2 expression in infiltrated leukocytes. In addition, human neutrophils exposed to P. gingivalis also upregulated COX-2 expression. Blood borne P. gingivalis gave significant increases in the murine tissue levels of COX-2 mRNA associated with both heart and lungs, supporting a potential role for this oral pathogen in the evolution of systemic events. The administration of metabolically stable analogues of LX and of aspirin-triggered LX potently blocked neutrophil

traffic into the dorsal pouch cavity and lowered PGE(2) levels within exudates. Together, these results identify PMN as an additional and potentially important source of PGE(2) in periodontal tissues. Moreover, they provide evidence for a novel protective role for LX in periodontitis, limiting further PMN recruitment and PMN-mediated tissue injury that can lead to loss of inflammatory barriers that prevent systemic tissue invasion of oral microbial pathogens.

L28 ANSWER 6 OF 8 MEDLINE
ACCESSION NUMBER: 1999280102 MEDLINE
DOCUMENT NUMBER: 99280102 PubMed ID: 10353635
TITLE: Inhibition of human sPLA2 and **5-lipoxygenase** activities by two neo-clerodane diterpenoids.
AUTHOR: Benrezzouk R; Terencio M C; Ferrandiz M L; San Feliciano A; Gordaliza M; Miguel del Corral J M; de la Puente M L; Alcaraz M J
CORPORATE SOURCE: Department of Pharmacology, University of Valencia, Spain.
SOURCE: LIFE SCIENCES, (1999) 64 (19) PL205-11.
Journal code: 0375521. ISSN: 0024-3205.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990618
Last Updated on STN: 19990618
Entered Medline: 19990610

AB The inhibitory effect of two neo-clerodane diterpenoids, E-isolinaridial (EI) and its methylketone derivative (EIM), isolated from Linaria saxatilis var. glutinosa, on PLA2 and other enzyme activities involved in the inflammatory process was studied. Both compounds inhibited human synovial sPLA2 in a concentration-dependent manner with IC50 values of 0.20 and 0.49 microM, respectively, similar to scalaradial. Besides, these compounds decreased the cell-free **5-lipoxygenase** activity and A23187-induced neutrophil LTB4 biosynthesis. Another function of human neutrophils, such as receptor-mediated degranulation, was also significantly reduced. In contrast, none of the compounds affected superoxide generation in leukocytes, or cyclooxygenase-1, **cyclooxygenase-2** and inducible nitric oxide synthase activities in cell-free assays.

L28 ANSWER 7 OF 8 MEDLINE
ACCESSION NUMBER: 1999143825 MEDLINE
DOCUMENT NUMBER: 99143825 PubMed ID: 9989280
TITLE: Affinities of various mammalian arachidonate lipoxygenases and cyclooxygenases for molecular oxygen as substrate.
AUTHOR: Juranek I; Suzuki H; Yamamoto S
CORPORATE SOURCE: Department of Biochemistry, Tokushima University School of Medicine, Japan.
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (1999 Jan 4) 1436 (3) 509-18.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990316
Last Updated on STN: 19990316

Entered Medline: 19990304

AB In an attempt to study affinities for molecular oxygen of mammalian arachidonate oxygenases, which remain unclarified at present, we determined activities of platelet-type 12-lipoxygenase, **leukocyte**-type 12-lipoxygenase, **5-lipoxygenase**, 15-lipoxygenase, cyclooxygenase-1 and **cyclooxygenase-2** at various oxygen concentrations. Activities of all the tested enzymes were assessed by oxygenation of radioactive arachidonic acid under hypoxic conditions, and part of the enzymes were also assayed by monitoring oxygen consumption. Their Km values for oxygen ranged between 10 and 26 microM. These results should be considered in investigations of arachidonic acid metabolism in pathophysiological processes associated with hypoxia.

L28 ANSWER 8 OF 8 MEDLINE
ACCESSION NUMBER: 97404293 MEDLINE
DOCUMENT NUMBER: 97404293 PubMed ID: 9262379
TITLE: Evaluation of the antiinflammatory activity of a dual **cyclooxygenase-2** selective/**5-lipoxygenase** inhibitor, RWJ 63556, in a canine model of inflammation.
AUTHOR: Kirchner T; Argentieri D C; Barbone A G; Singer M; Steber M; Ansell J; Beers S A; Wachter M P; Wu W; Malloy E; Stewart A; Ritchie D M
CORPORATE SOURCE: The R.W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey 08869, USA.
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1997 Aug) 282 (2) 1094-101.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970922
Last Updated on STN: 19970922
Entered Medline: 19970911

AB Sterile perforated polyethylene spheres (wiffle golf balls) were implanted s.c. in beagle dogs. A local inflammatory reaction was elicited within the spheres by injecting carrageenan. Changes in **leukocyte** count, prostaglandin E2, thromboxane B2 and leukotriene B4 levels were monitored in fluid samples collected over a 24-hr period. Blood samples were also collected at various time points and analyzed for prostaglandin E2 and leukotriene B4 production after ex vivo calcium ionophore treatment. Effects of standard antiinflammatory agents (aspirin, indomethacin, dexamethasone, tenidap and zileuton) and newer **cyclooxygenase-2** (COX-2) selective agents (nimesulide, nabumetone and SC-58125) were determined after oral administration. Ex vivo inhibition of cyclooxygenase product synthesis (prostaglandin E2, thromboxane B2) in whole blood was used as an indicator of activity for the constitutive COX-1 isoform, although inhibition of the synthesis of these mediators in the chamber exudate during an inflammatory process is believed to represent COX-2 inhibition. Treatment effects on leukotriene B4 production were also determined both ex vivo in whole blood and in the fluid. All of the compounds tested, except aspirin, inhibited **leukocyte** infiltration into the fluid exudate. Inhibitors that exert their effects on both isozymes of cyclooxygenase attenuate production of cyclooxygenase metabolites in both the inflammatory exudate and in peripheral blood ex vivo, although COX-2 selective inhibitors only demonstrated activity in the exudate. A **5-lipoxygenase** inhibitor (zileuton), a corticosteroid (dexamethasone) and a dual COX-2 selective/**5-**

lipoxygenase inhibitor (RWJ 63556) had similar profiles in that they all inhibited cell infiltration and eicosanoid production in the fluid and also attenuated leukotriene B4 production in both the fluid and blood.

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(FILE 'HOME' ENTERED AT 14:16:36 ON 09 JUL 2002)

FILE 'CA' ENTERED AT 14:16:42 ON 09 JUL 2002

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L1          2999 S CYCLOOXYGENASE 2
L2          2287 S L1 AND INHIBIT?
L3             2 S 5 LIPOXYGENEASE INHIBIT?
L4          4077 S 5-LIPOXYGENASE
L5         13166 S IMMUNOSUPPRESSIVE
L6          1047 S ANTI-PROLIFERATIVE
L7             1 S ANIT-INFLAMMATORY
L8         60635 S LEUKOCYTE
L9         74230 S L5 OR L6 OR L7 OR L8
L10            0 S L9 AND L1 AND L3
L11            8 S L9 AND L1 AND L4
L12           61 S L1 AND L4
L13           95 S L1 AND L9
L14          589 S L4 AND L9
L15            8 S L12 AND L13
L16            7 S L12 AND COMBIN?
L17           10 S L13 AND COMBIN?
L18            1 S L15 AND COMBIN?
L19           16 S L16 OR L17 OR L18
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FILE 'MEDLINE' ENTERED AT 14:29:21 ON 09 JUL 2002

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L20         3883 S L1
L21         3095 S L4
L22        49173 S L5
L23         1140 S L6
L24            2 S L7
L25        83095 S L8
L26       131838 S L22 OR L23 OR L24 OR L25
L27           61 S L20 AND L21
L28            8 S L27 AND L26
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---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

STN INTERNATIONAL LOGOFF AT 14:30:30 ON 09 JUL 2002